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Glycemic control and outcome related to cardiopulmonary bypass

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Abstract

Perioperative hyperglycemia, aggravated by cardiopulmonary bypass, is associated with adverse outcome in adult and pediatric patients. Whereas hyperglycemia was originally perceived as an adaptive response to surgical stress, it is now clear that glycemic control is a strategy to reduce adverse outcomes after cardiac surgery and cardiopulmonary bypass. The optimal blood glucose target, whether or not glycemic control should be initiated already intraoperatively and whether or not perioperative glucose administration affects the impact of glycemic control on ischemia-reperfusion damage remain open questions. Hypoglycemia, the risk of which is increased with glycemic control, is also associated with adverse outcome. However, it remains controversial whether brief episodes of hypoglycemia, rapidly corrected during glycemic control, have adverse effects on outcome. This review gives an overview of the currently available literature on glycemic control during and after cardiac surgery and focuses on the indicated open questions about this intervention for this specific patient population.

Key words

Hyperglycemia, critical care, cardiac surgery, cardiopulmonary bypass, glycemic control, intensive insulin therapy, hypoglycemia, glucose variability

A. Hyperglycemia in cardiac surgery patients

Hyperglycemia is a commonly occurring metabolic disturbance in patients who undergo cardiac surgery, whether or not suffering from pre-existing diabetes mellitus (1). The use of cardiopulmonary bypass (CPB) for cardiac surgery further disturbs glucose homeostasis and aggravates the hyperglycemic response (2). Although any blood glucose value higher than the normal healthy range during cardiac surgery could be labeled as hyperglycemia, a clear definition of perioperative hyperglycemia is currently lacking (3). However, the American Diabetes Association suggests defining any blood glucose value above 140 mg/dl (>7.8 mmol/l) in the perioperative phase as perioperative hyperglycemia (4).

Several factors contribute to the hyperglycemic response evoked by cardiac surgery. These include the patient's predisposition, metabolic alterations induced by the injury of the surgery and concomitant treatments. Patient's characteristics that predispose to a more severe hyperglycemic response include the presence of obesity, insulin resistance, hypertension and an atherogenic lipid profile, which are all highly prevalent among cardiac surgery patients (5). The development of a sort of "diabetes of injury" or "stress diabetes" during cardiac surgery is characterized by insulin resistance, which contributes to the degree of perioperative hyperglycemia (6). The exact pathophysiology of this "stress hyperglycemia" is complex and reviewed extensively elsewhere (6). Furthermore, several commonly used anesthesiologic interventions during cardiac surgery may disturb glucose metabolism. These include the administration of inotropes, vasopressors, glucocorticoids, heparin, beta-blockers and the infusion of glucose (7).

The hyperglycemic response to surgery was long considered to be adaptive and beneficial. This was based on the assumption that high levels of circulating glucose would fuel the high glucose need of cells that predominantly rely on glucose as metabolic substrate and that can take up

glucose independent of insulin, such as neurons, hepatocytes, endothelial cells and blood cells. This viewpoint, however, contrasted with the clear association between hyperglycemia and increased morbidity and mortality as observed for critically ill patients (8-10) and cardiac surgery patients (11-13). This evidence has recently been summarized in a systematic review (3). These findings suggested that cardiac surgery-induced hyperglycemia, rather than being an adaptive response and reflecting the severity of the surgical procedure or pharmalogical interventions, may contribute to complications. This alternative interpretation provided the rationale for lowering blood glucose concentrations during the perioperative period in cardiac surgery patients.

B. Glycemic control in cardiac surgery patients

Several studies have investigated the impact of lowering blood glucose concentrations in cardiac surgery patients. These are discussed separately for adult and pediatric patients in the following sections and summarized in Table 1.

a. Adult cardiac surgery patients

The first randomized controlled trial (RCT) to investigate the effect of lowering glycemia in the perioperative period was published in 2001 (14). In this single center study 1,548 adult patients were randomized to receive either intensive insulin therapy (IIT) in which insulin was infused to target blood glucose to the normal range of 80-110 mg/dl (4.4-6.1 mmol/l) or to conventional therapy with infusion of insulin only when glucose concentrations exceeded 215 mg/dl (11.9 mmol/l). The latter was the standard of care at that time for patients admitted to the surgical intensive care unit (ICU). In this study, 63% of the patients were admitted to the ICU after cardiac surgery. IIT reduced mortality of the total group of ICU patients, as well as of the cardiac surgery subgroup (15). In the latter subgroup, the mortality benefit was maintained up to 4 years after hospital discharge. Morbidity of the cardiac surgery patients was also reduced, most pronounced for patients who stayed more than 3 days in the ICU, as indicated by earlier weaning from mechanical ventilation, less acute renal failure, reduced incidence of critical illness polyneuropathy, reduced inflammation and shorter ICU stay (15). Similar findings have been reported in observational studies by Furnary et al. (16). In these studies, 3,554 patients with pre-existing diabetes mellitus who underwent coronary artery bypass grafting between 1987 and 2001 were described. These reports showed a 50% decrease in perioperative mortality and a significant decrease in the incidence of deep sternal wound infections in patients receiving

continuous insulin infusion with a blood glucose target of 100-150 mg/dl (5.6-8.3 mmol/l). The authors further expanded the patient cohort between 2001 and 2005 to include an additional 1,980 patients (17). In this study, tighter glycemic control resulted in a decreased incidence of deep sternal wound infections, hospital length of stay, blood transfusions, new onset atrial fibrillation and low cardiac output syndrome (17). A study by Lazar et al. confirmed these observations (18). In this study, 141 diabetic patients undergoing coronary artery bypass grafting (CABG) were randomized to receive glycemic control with a blood glucose target of 125 to 200 mg/dl (6.9-11.1 mmol/l), or standard therapy (blood glucose target <250 mg/dl or <13.9 mmol/l). The patients randomly allocated to the tighter glycemic control achieved lower blood glucose levels (138+/-4 versus 260+/-6 mg/dl), which resulted in a reduced incidence of atrial fibrillation and wound infections, a shorter postoperative length of hospital stay and a survival advantage 2 years after surgery.

However, the enthusiasm about the use of glycemic control in the perioperative period was tempered by the findings of the NICE-SUGAR trial (19). This prospective, multi-center RCT included 6,104 general ICU patients who were randomized to a blood glucose target of 81-108 mg/dl (4.5-6.0 mmol/l) (IIT) or 144-180 mg/dl (8-10 mmol/l). The control group of NICE-SUGAR was thus treated quite differently from those in the earlier proof-of-concept studies as most patients also received a form of glycemic control. IIT, as compared with the control group of this study, increased mortality from 24.9% to 27.5%. It should be noted, however, that only 37% of the studied patients in NICE-SUGAR were surgical ICU patients and only few, if any, cardiac surgery patients were included. Hence, the relevance of the NICE-SUGAR findings for the cardiac surgery population remains debated. Moreover, this study was further confounded by a significant overlap between the glucose concentrations that were achieved in the two groups and by the use of inaccurate blood glucose measurement tools, making it difficult to correctly interpret the results (20). Therefore, the standard of care for adult patients who

underwent cardiac surgery with or without CPB still includes careful glycemic control, as advised by current guidelines (21).

1. Timing and duration of the intervention

Glycemic control in cardiac surgery patients was first applied only in the postoperative period, i.e. the ICU, where it showed to reduce morbidity and mortality (14). However, also the presence of intraoperative hyperglycemia has been shown to correlate with higher morbidity and mortality (11,12,22), suggesting that additional intraoperative glycemic control could possibly be beneficial. Several observational studies reported protocols for glycemic control in the intraoperative and postoperative period, with beneficial effects on mortality and morbidity, suggesting that intraoperative glycemic control is safe and feasible (17,18,23). Interestingly, the effect of IIT appeared to depend on the length of time it was applied, with a minimum of 3 days apparently required for an appreciable benefit (14-16). Hence, it remained an open question whether expanding glycemic control to the intraoperative period, for an additional 3-4 h, provides any additional benefit as compared with only postoperative glycemic control. This question was addressed in a study by Gandhi et al. (24). This study showed no additional benefit of intraoperative glycemic control, when postoperative glycemic control is maintained. However, as the study was underpowered to detect a small additional effect, the question remains unanswered (25). Therefore, the addition of intraoperative glycemic control, when postoperative glycemic control is provided, remains experimental and should only be used in centers with sufficient experience in targeting and achieving normoglycemia during cardiac surgery. Further studies are needed to establish any role of intraoperative glycemic control during cardiac surgery.

2. Blood glucose target range

The exact target for blood glucose concentrations in ICU patients has been the subject of considerable debate. Recent results of large RCTs have clearly shown that a "one size fits all" policy may not be applicable for glycemic control in ICUs worldwide. For cardiac surgery patients, current guidelines advocate keeping blood glucose concentrations below 180 mg/dl (10 mmol/l) in the perioperative period (21). However, the randomized controlled study that provided the first evidence in favor of blood glucose control after cardiac surgery targeted strict normoglycemia (80-110 mg/dl or 4.4-6.1 mmol/l) and found this to be effective (14). Whether targeting higher blood glucose levels (110-180 mg/dl) in cardiac surgery patients is equally effective for survival is unclear as no adequately powered RCTs have been done to address this specific question.

Recently it also has become clear that targeting strict normoglycemia (80-110 mg/dl) in ICU patients with pre-existing diabetes mellitus is not associated with similar benefits as was observed for patients without a history of diabetes and may even be harmful in this population (26). These findings suggest that patients suffering from diabetes who are not perfectly treated to normoglycemia have developed a certain tolerance or adaptation to a moderate degree of hyperglycemia. Such adaptation may occur at the level of expression of glucose transporters in different cell types (27,28). When acutely targeting strict normoglycemia in the perioperative period for such patients, this could evoke an acute derangement of this new homeostasis, with insufficient cellular glucose uptake as a consequence, which could be harmful. Results of several studies support this possibility for diabetic patients undergoing cardiac surgery. Furnary et al. reported a benefit from targeting mild hyperglycemia instead of strict normoglycemia for patients with diabetes mellitus (16) and in the Leuven surgical ICU study, there was a clear benefit when targeting strict normoglycemia in predominantly non-diabetic patients, whereas

those with pre-existing diabetes mellitus did not appear to benefit (14). In the light of these findings, it may be useful to obtain hemoglobin A1c (HbA1c), a glycosylated hemoglobin, prior to cardiac surgery (21). HbA1c, an indicator of the average level of glycemia over the previous 2 to 3 months, has been shown to be frequently elevated in patients, with or without known diabetes mellitus, undergoing cardiac surgery (29). HbA1c has been shown to tightly correlate with average blood glucose levels and may therefore be used to decide on the optimal target for perioperative blood glucose control (30). Further research is warranted to investigate these open questions, in a prospective randomized controlled way. Since such studies are currently not available yet, it may be wise to tolerate mild hyperglycemia in patients with a history of diabetes mellitus, more specifically to the level of blood glucose these patients were used to have before they underwent surgery, and to only target strict normoglycemia for patients without a history of diabetes.

3. Nutritional support

One of the major risks of cardiac surgery, with or without the use of CPB, is the impact of transient ischemia-reperfusion on the myocardium. More than fifty years ago, Dr. Sodi-Pallares suggested a metabolic strategy to protect the myocardium from the deleterious effects of ischemia-reperfusion (31). This strategy comprised the infusion of glucose, insulin and potassium which was called “GIK therapy”. The rationale for this intervention was to shift substrate utilization in the ischemic myocardium from fatty acids to glucose for anaerobic glycolysis, whereby reducing oxygen consumption in turn reducing ischemia-reperfusion damage in the myocardium. Furthermore, the increased influx of potassium in the myocardium by means of insulin and glucose infusion would reduce the risk of malignant arrhythmias and insulin could mediate cardioprotection (32).

Several large trials addressing the use of GIK therapy during cardiac surgery were conducted, yielding contradictory results (33). These studies were, however, obscured since different "GIK cocktails" were used in the different studies and blood glucose was unaffected, resulting in profound hyperglycemia in some studies. Therefore, a negative effect of the concomitant hyperglycemia may have overruled any possible protective effect of GIK therapy (34). This question was addressed by an elegant study by Carvalho et al. (35). In this study, patients were randomly allocated to a group receiving GIK therapy while targeting normoglycemia, called GIN therapy (N stands for normoglycemia), or to a group receiving standard care. GIN therapy clearly protected the myocardium during cardiac surgery, suggesting that normoglycemia may be the crucial factor of GIK/GIN therapy.

One could question whether the infusion of glucose is in fact required to obtain the cardioprotection from targeting normoglycemia with insulin infusion (34). The infusion of glucose might even be deleterious, since macronutrients and insulin are potent inhibitors of autophagy, a crucial cellular housekeeping machinery responsible for the removal of toxic protein aggregates and damaged organelles (36). Recent findings of a large RCT investigating the effect of early parenteral nutrition in patients admitted to the ICU, referred to as the EPaNIC study, may shed some light on this question (37). In this study, the effect of early parenteral supplementation of insufficient enteral feeding on morbidity and mortality of ICU patients was examined. In one study arm, a 20% glucose infusion was administered on the admission day and the day after, resulting in a total energy intake of about 400 kcal on day 1 and 800 kcal on day 2. From the morning of day 3 onwards, all-in-one parenteral nutrition was started when necessary to reach the caloric goal. Patients who were randomized to the other study arm only received 5% glucose solution in an equal volume to that of the early-initiation group to provide adequate hydration, and for them the severe macronutrient deficit that accumulated over the first week was accepted. In this group, all-in-one parenteral nutrition was only initiated beyond

day 8 and only if enteral nutrition was still insufficient at that time. In both study arms, normoglycemia was maintained. Of the 4,640 included patients, 63% were cardiac surgery patients. Withholding early parenteral nutrition had no effect on mortality, but decreased the rate of new ICU infections, lowered the incidence of cholestastis and reduced the duration of mechanical ventilation, of renal replacement therapy and of ICU stay, as well as the incidence of clinically relevant muscle weakness (37,38). This study clearly showed that early provision of macronutrients while maintaining normoglycemia has no beneficial effects and even causes excess harm. Therefore, it appears wise not to provide high doses of glucose while preserving normoglycemia with insulin infusion in cardiac surgery patients. Further research is required to investigate specifically whether or not perioperative administration of glucose, when normoglycemia is maintained, results in myocardial protection against ischemia-reperfusion injury.

b. Pediatric cardiac surgery patients

Hyperglycemia is also prevalent in children undergoing cardiac surgery and also in this patient population the degree of hyperglycemia has been associated with adverse outcome (39). Whether glycemic control in pediatric cardiac surgery patients during the perioperative period is beneficial, as shown in the adult population, was first studied by Vlasselaers et al. (40). In this study 700 critically ill patients were randomized to receive IIT to obtain age-adjusted normoglycemia (50-80 mg/dl (2.8-4.4 mmol/l) in infants and 70-100 mg/dl (3.9-5.6 mmol/l) in children) or to tolerating hyperglycemia up to 215 mg/dl (11.9 mmol/l). The studied population comprised a predominantly surgical population, with 75% of the patients being included after cardiac surgery for congenital heart defects. IIT in this pediatric ICU population reduced the inflammatory response, lowered the postoperative levels of troponin and heart-type fatty acid binding protein, reduced the rate of secondary infections, shortened ICU stay, and improved ICU survival. IIT also increased the occurrence of hypoglycemia, but this did not have a negative effect on the acute outcomes nor on the neurocognitive development at 4 years follow-up (40,41). In fact, IIT had a positive effect on cognitive executive functions after 4 years, such as motor coordination and cognitive flexibility (41). The same investigators showed that targeting age-adjusted normoglycemia during and after cardiac surgery in neonates protected the myocardium and reduced the inflammatory response (42). Recently, two other RCTs on glycemic control in pediatric cardiac surgery patients were performed. The first study, the SPECS study, was a two-center RCT which included 980 children after cardiac surgery with CPB, most of them younger than 1 year (43). The RCT targeted blood glucose concentrations of 80-110 mg/dl (4.4–6.1 mmol/l), a level much higher than the age-adjusted normoglycemia range for the studied children, in one group as compared with virtually no glucose management in the other group and did not find an effect on infections or mortality. However, important differences between this study and the first pediatric RCT complicate interpretation of these

findings (44). First, the blood glucose target in the intervention arm (80-110 mg/dl, reached in only about 50% of the patients) of the SPECS study was not “normal for age” and therefore age-adjusted normoglycemia was not achieved. In fact, the majority of the children in the control group spontaneously reached the targeted blood glucose level of the intervention arm, which reflected hyperglycemia for that age-group, and therefore blood glucose concentrations in the 2 study arms were only slightly and very transiently different, a difference that was not clinically relevant. Interestingly, in a post-hoc analysis the investigators of the SPECS trial did find a reduced incidence of infections with targeting lower, but not normal for age, glycemia in older patients (45). The second study, the CHiP trial, was a multi-center study that included 1,369 critically ill children of which 60% had undergone cardiac surgery. Patients were randomized to achieve glycemic control targeting blood glucose to 72-126 mg/dl (4-7 mmol/l), a blood glucose range that was again higher than the normal range for the age-group, or to tolerating glycemia up to 215 mg/dl (11.9 mmol/l) (46). This study again showed very minor effects on blood glucose concentrations, with transient differences being smaller than the error of the measurement tools, and not unexpectedly, found no effect on mortality. Nevertheless, randomization to glycemic control lowered length of stay in the hospital and reduced the incidence of kidney failure. Again, due to the chosen target for blood glucose in this trial, the expected effect size was an overestimation and hence the study was not statistically powered to detect any benefit from such a small difference in blood glucose (47). In conclusion, current evidence still supports careful targeting of blood glucose levels that are “normal for age” in the perioperative setting in pediatric cardiac surgery patients. Further research is needed to investigate several other aspects of glycemic control in pediatric patients. These comprise, among others, the optimal duration of treatment needed to obtain benefits as well as the role of concomitant nutritional support.

C. Hypoglycemia and glycemic variability

Treating hyperglycemia in the ICU with insulin inherently increases the incidence of hypoglycemia, as was uniformly shown in all RCTs that studied this intervention (14,19,48). Whether this increased incidence of hypoglycemia is detrimental, has been a topic of considerable debate. Whereas it is commonly accepted that severe and prolonged hypoglycemia increases morbidity and mortality, this is not clear for short-lasting, iatrogenic hypoglycemia in the ICU (4). In the first Leuven study of surgical ICU patients, among which many cardiac surgery patients, the incidence of hypoglycemia in the IIT group rose from 0.8% to 5.1% (14). However, hypoglycemia was never associated with immediate mortality in this study. Interestingly, a recent retrospective cohort study showed that only spontaneous, but not iatrogenic hypoglycemia is associated with an increased mortality risk (49). These findings suggest that hypoglycemia may be more a sign of severity of illness, but not necessarily an inducer of harm, as long as hypoglycemia is short lasting. This viewpoint is supported by other studies. Quantification of circulating markers of neuronal and astrocyte damage in the Leuven pediatric ICU study showed that patients experiencing a brief hypoglycemic episode had elevated levels of these markers already *before* the hypoglycemic event, with no increase in these markers evoked by the hypoglycemic event, making it unlikely that hypoglycemia caused damage to these cells (50). A recent retrospective study of cardiac surgery patients receiving IIT showed that patients who developed hypoglycemia also had an increased risk of respiratory complications, prolonged ICU and hospital stay, which again might indicate that hypoglycemia occurs in the sicker patients (51). Interestingly, in this study hypoglycemia was not associated with mortality. The most convincing evidence that iatrogenic short-lasting hypoglycemia did not induce excess harm was generated by the long-term follow-up of the children included in the Leuven pediatric ICU study (41). In this study, randomization to IIT resulted in an increased

incidence of hypoglycemia below 40 mg/dl from 1% to 25%, but this did not result in a worse score on any measure of cognitive function at four years follow-up. Actually, the IIT group scored better for motor coordination and cognitive flexibility. Even though short-lasting hypoglycemia most likely did not induce harm in this study, this may be due to the fact that all measures were taken to quickly and adequately correct it.. In order to prevent hypoglycemia when targeting normoglycemia, and hereby increasing the safety of IIT, it is obligatory to use an intravenous insulin drip and to measure the glycemia frequently with appropriate measuring tools, as was recently acknowledged in a consensus statement (52). Extending intervals for blood glucose measurement beyond 2h increases the risk of serious hypoglycemic events. Therefore, caution is advocated when increasing the interval. Recently, several risk factors contributing to hypoglycemia during cardiac surgery have been identified. These included female gender, pre-existing diabetes mellitus, the application of hemodialysis and intraoperative blood product transfusion (51). Therefore, it may be wise to monitor glycemia more frequently in these patients undergoing cardiac surgery.

Another point of interest is glucose variability. Irrespective of blood glucose control, glucose variability is closely associated with the risk of death in critically ill patients (53-56) and in cardiac surgery patients (11). Factors contributing to glycemic variability include intrinsic and extrinsic patient factors. For example, patients with a pre-morbid deranged glucose homeostasis are more at risk to experience fluctuating glucose levels (57). Examples of extrinsic factors are the mode of insulin administration (higher glycemic variability with the use of subcutaneous insulin administration), nutritional support and the applied glycemic control algorithm. It is possible that glycemic variability could have contributed to the different outcomes of the studies on glycemic control during/after cardiac surgery, since it has been shown that protocols differ significantly in their ability to keep patients within the desired range (58). Furthermore, recent evidence points out that hyperglycemia after hypoglycemia may be more detrimental rather

than the hypoglycemic event itself (59). The fact that in the Leuven studies, also in the critically ill children, rebound hyperglycemia after hypoglycemia was carefully avoided, may be a very important safety aspect in this regard (40).

In conclusion, whereas severe and prolonged hypoglycemia is considered to be detrimental and should be avoided, current evidence points out that the occurrence of mild and short lasting hypoglycemia during glycemic control in the ICU does not have a detrimental effect on outcome in the context of careful and frequent monitoring and with use of performant control algorithms. Further research is needed to identify the role of glycemic variability in cardiac surgery patients and to identify new techniques to minimize the rate of hypoglycemic events and high glycemic variability, such as continuous glucose measurement tools, the use of a validated blood glucose control algorithm (60) and possibly also the use of drugs other than insulin to lower blood glucose.

D. Summary

Based on the available evidence, careful and effective glycemic control in combination with delaying any parenteral nutrition to beyond the first postoperative week, can be advised to prevent additional metabolic damage to patients undergoing cardiac surgery, with or without CPB. Currently, evidence is lacking for additional intraoperative glycemic control if postoperative glycemic control is provided. For patients without a history of diabetes mellitus, age-adjusted normoglycemia is probably the most effective blood glucose target range. However, when the logistics and the experience to achieve safe glycemic control are not available, tolerating mild hyperglycemia up to 180 mg/dl and delaying any parenteral nutrition, may be a defendable option, based on common sense. For patients with a history of diabetes mellitus, it may be better to tolerate mild hyperglycemia, instead of targeting strict normoglycemia. More research on glycemic control for cardiac surgery patients, with or without CPB, is necessary in order to further optimize the care for these patients.

Practice points

- Pronounced hyperglycemia in the perioperative period of patients undergoing cardiac surgery is detrimental and should be prevented with insulin treatment.
- In order to apply glycemic control in cardiac surgery patients, one should measure blood glucose concentrations frequently with appropriate measuring tools and use a well validated guideline/algorithm for insulin titration.
- A “one size fits all” blood glucose target range may not apply for all cardiac surgery patients.
- For patients without a history of diabetes mellitus, current evidence supports targeting normoglycemia (80-110 mg/dl) without the use of early parenteral nutrition. If appropriate logistics are not available to do this in a safe way, accepting somewhat higher blood glucose levels is to be advised.
- For patients with diabetes mellitus, current evidence supports a somewhat higher target range or blood glucose control in the perioperative setting.

Research agenda

- The role of glucose supplementation, when normoglycemia is provided, in preventing myocardial ischemia-reperfusion damage during cardiac surgery should be further investigated.
- Several aspects of glycemic control in the pediatric population, such as optimal timing, duration and the effect of combination with nutritional support, should be examined.
- The role of techniques to minimize the rate of hypoglycemic events and high glycemic variability, such as continuous glucose measurement tools, the use of validated blood glucose control algorithms and possibly also the use of drugs other than insulin to lower blood glucose, should be defined.

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Conflict of interest

None

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Table1. Impact of glycemic control in studies that included cardiac surgery patients

Glycemic control in adult cardiac surgery patients			
	Van den Berghe et al. 2001 (14)	*Furnary et al. 2006 (17)*	*Lazar et al. 2009 (21)*
Type of study	Randomized controlled trial	Observational study	Randomized controlled trial
Patient population	Surgical ICU	Cardiac surgery patients	Cardiac surgery patients
- *No. of cardiac surgery patients*	970 (of 1,548)	5,534	141
- *% of patients with history of diabetes*	16	100	100
Intervention arm			
- *Blood glucose target*	80-110 mg/dl (4.4-6.1 mmol/l)	100-150 mg/dl (5.6-8.3 mmol/l)	125-200 mg/dL (6.9-11.1 mmol/l)
- *Therapy*	i.v. insulin administration	i.v. insulin administration	s.c. insulin administration
- *Blood glucose reached*[$]	103 mg/dl (5.7 mmol/l)	121 mg/dl (6.7 mmol/l)[+]	138 mg/dl (7.7 mmol/l)
Control arm			
- *Blood glucose target*	Tolerating hyperglycemia up to 215 mg/dl (11.9 mmol/l)	Historical controls	Tolerating hyperglycemia up to 250 mg/dl (13.9 mmol/l)
- *Blood glucose reached*[$]	153 mg/dl (8.5 mmol/l)	>200 mg/dl (11.1 mmol/l)	260 mg/dl (14.4 mmol/l)
Effect of intervention on outcome	- Decreased mortality* - Fewer bloodstream infections° - Decrease in need for renal replacement therapy*° - Reduced inflammatory response° - Fewer blood transfusions - Shorter length of ICU stay° - Shorter duration of ventilatory support° - Less hyperbilirubinaemia*° - Less polyneuropathy*°	- Decreased mortality - Less atrial fibrillation - Fewer wound infections - Shorter length of hospital stay - Fewer blood transfusions	- Decreased mortality - Less atrial fibrillation - Fewer wound infections - Shorter length of hospital stay
Glycemic control in pediatric cardiac surgery patients			
	Vlasselaers et al. (40)	*Agus et al. (43)*	*Macrae et al. (46)*
Type of study	Randomized controlled trial	Randomized controlled trial	Randomized controlled trial
Patient population	Mixed PICU	Cardiac surgery patients	Mixed PICU
- *No. of cardiac surgery patients*	526 (of 700)	980	837 (of 1,369)
Intervention arm			
- *Blood glucose target*	Age-adjusted normoglycemia * Infants: 50-80 mg/dl (2.8-4.4 mmol/l) * Children: 70-100 mg/dl (3.9-5.6 mmol/l)	80-110 mg/dl (4.4-6.1 mmol/l)	72-126 mg/dl (4-7 mmol/l)
- *Therapy*	i.v. insulin administration	i.v. insulin administration	i.v. insulin administration
- *Blood glucose reached*[$]	* Infants: 86.4 mg/dl (4.8 mmol/l) * Children: 95.4 mg/dl (5.3 mmol/l)	109 mg/dl (6 mmol/l)	105 mg/dl (5.8 mmol/l)
Control arm			
- *Blood glucose target*	Tolerating hyperglycemia up to 215 mg/dl (11.9 mmol/l)	Standard care (no target range, treated according to the discretion of the physician)	Tolerating hyperglycemia up to 215 mg/dl (11.9 mmol/l)
- *Blood glucose reached*[$]	* Infants: 115.2 mg/dl (6.4 mmol/l) * Children: 147.6 mg/dl (8.2 mmol/l)	113 mg/dl (6.3 mmol/l)	112 mg/dl (6.2 mmol/l)
Effect of intervention on outcome	- Decreased mortality - Reduced inflammatory response - Lower postoperative levels of troponin* - Reduced rate of secondary infections - Shorter ICU stay	- No effect on mortality - No effect on morbidity	- No effect on mortality* - Decrease in need for renal replacement therapy* - Lower total health care costs

* Effect of the intervention on outcome was also reported for the cardiac surgery patient subgroup. ° Effect of the intervention on outcome was also reported for cardiac surgery patients who stayed in ICU for at least a third day. $ Mean blood glucose concentration reached; if mean blood glucose concentration was not stated in the article, mean blood glucose concentration was estimated from the provided figures. $^{+}$Mean achieved blood glucose concentration achieved during the calendar year 2005.